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OMEGA-3 FATTY ACIDS AND BLOOD PRESSURE

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Abstract – There is substantial evidence that ω3 fatty acids reduce blood pressure, with a greater effect in hypertensive patients and those with high-normal blood pressure. The dose of ω3 fatty acids required to achieve a blood pressure reduction is likely to be at least 3-4 g/day. However, the magnitude of the blood pressure change can be increased by salt restriction or when ω3 fatty acids are incorporated into a weight reducing program. It is also highly plausible that increased ω3 fatty acid consumption as part of a dietary change including increased consumption of fruits and vegetables, and moderation of salt intake, will confer significant cardiovascular benefit.

Key words: Omega-3 fatty acids, blood pressure, hypertension, vascular function.

INTRODUCTION

There is considerable evidence from clinical, experimental and epidemiological studies that omega-3 (ω3) fatty acids derived from fish and fish oils, are protective against atherosclerotic heart disease and sudden coronary death (56,73,74). ω3 Fatty acids have multiple effects leading to improvements in blood pressure (1,3,26,60) and cardiac function (44), arterial compliance (52,62), vascular reactivity (9,58), lipids and lipid metabolism (32,33), reduced leukocyte-derived cytokine formation (8), and anti-platelet (40) and anti-inflammatory effects (8,57). There is also evidence from studies in humans that eicosapentaenoic acid (EPA, 20:5 ω3) and docosahexaenoic acid (DHA, 22:6 ω3), the two main ω3 fatty acids, have differential effects on blood pressure, heart rate, lipids and vascular reactivity (59).

Abbreviations: ADP, Adenosine diphosphate; **ATP,** Adenosine triphosphate; **DBP,** Diastolic blood pressure; **DHA,** Docosahexaenoic acid; **EPA,** Eicosapentaenoic acid; **NO,** Nitric oxide; **PGI,** Prostagladin I; **SBP,** Systolic blood pressure; **SHR,** Spontaneously Hypertensive Rat; **TXA,** Thromboxane.

Numerous population studies have shown an inverse association between ω3 fatty acids and cardiovascular disease. A meta-analysis by Wang et al (84) showed that increased consumption of ω3 fatty acids from fish or fish oil supplements reduces the rates of all-cause mortality, cardiac and sudden death and possibly stroke. These findings are in accord with meta-analyses by Bucher et al (7), He et al (38) and Whelton et al (85) that provide further support of an inverse association between ω3 and coronary heart disease. An inverse association between increasing intakes of ω3 fatty acids and risk of stroke, particularly ischemic stroke, was also demonstrated in a meta-analysis by He et al (37).

This paper reviews the evidence for effects of omega-3 fatty acids on blood pressure in humans. Some animal data will be considered where it assists to understand possible mechanisms of action of omega-3 fatty acids.

POPULATION STUDIES

There is some evidence for benefits of fish consumption on blood pressure from population studies. A cross sectional comparison of Bantu fisherman with non fish eating Bantu farmers showed the former had a much lower increase in

blood pressure with ageing (66). Paradoxically the high incidence of hypertension in the Japanese population occurs despite their high fish intake, although this is likely due to their very high salt consumption. Panagiotakos et al (65) also recently report an inverse relationship between fish intake and systolic blood pressure (SBP), but not diastolic blood pressure (DBP), in a population of 300 men and women aged 65-100 years from the Mediterranean islands. The effect on SBP was maintained after adjusting for age, gender, educational status, physical activity level, BMI and smoking. Dietary habit including fish intake, estimated from food frequency questionnaires showed that at least 90% of participants consumed fish at least once a week and 61% of the participants reported they consumed fish approximately once a week for a mean period of 30 years. An inverse association was also observed between fish intake and the prevalence of hypertension. In particular, those individuals in the higher group of fish consumption were 15% less likely (p=0.02) to have hypertension. A limitation of this and other population studies, is that these associations may be explained to some extent by the fact that individuals with a healthy dietary pattern are also likely to have a healthy lifestyle.

META-ANALYSES

Randomised controlled intervention trials providing fish meals or supplementing fish oils unequivocally demonstrate that ω3 fatty acids lower blood pressure. Whilst some studies have reported no effect on blood pressure, this is likely due to study design, relatively small sample sizes leading to a lack of statistical power and / or an insufficiently high dose of ω3 fatty acids (1).

A number of meta-analyses have shown that ω3 fatty acids lower blood pressure. Morris et al (60), in a meta-analysis of 31 placebo controlled trials involving 1536 subjects, showed an overall reduction of –3.0/-1.5 mmHg with an average dose of 4.8g/day. The hypotensive effect was strongest in treated and untreated hypertensives (-3.4/-2.0 mmHg). Healthy subjects showed no significant change (-0.4/-0.7 mmHg). Large falls in blood pressure ranging from -10/-3 mmHg to -17/-10 mmHg were noted in studies including patients with cardiovascular disease. Significant dose-response effects were observed with doses of greater than 6g/day ω3 fatty acids leading to a predicted decrease of -0.66/-0.35 mmHg for each 1g/day increase in ω3 fatty acid supplementation. The dose response effect was greater for DHA (-1.5/-0.77 mmHg per g/day) than for EPA (-0.93/-0.53 mmHg per g/day).

Appel et al (1), estimated blood pressure fell -1.0/-0.5 mmHg in normotensives (data from 11 trials) and -5.5/-3.5 mmHg in untreated hypertensives (data from 6 trials), with the average intake being more than 3g/day of ω3 fatty acids. Although most of the trials used relatively large doses of ω3 fatty acids (greater than 3g/day) there was no significant dose response effect. The greater hypotensive effect and the smaller variation in results compared with data from the meta-analysis of Morris et al (60) may have been partly due to the exclusion of studies using treated hypertensives.

Geleijnse et al (26) conducted a meta-analysis of 36 trials in which 50% of participants were hypertensive (SBP $\geq$ 140 mmHg and / or DBP $\geq$ 90 mmHg), the mean trial duration was 11.7 years and the median dose of ω3 fatty acids was 3.7 g/day. Overall, ω3 fatty acids reduced blood pressure by -2.1/-1.6 mmHg. The blood pressure lowering effects also were greater in older (>45 years) (-3.5/-2.4) and hypertensive ($\geq$140/90 mmHg) (-4.0/-2.5) individuals.

A meta-analysis by Dickinson et al (19) examined the efficacy of dietary nutrients and lifestyle in patients with raised blood pressure. Data from 105 trials randomizing 6805 participants with a mean baseline blood pressure of 147/92 mmHg and a mean age of 50 years, showed that 0.1-1.7 g/day fish oil reduced blood pressure by -2.3/-2.2 mmHg. The effects were somewhat modest in comparison with the estimated benefits of improved diet (-5.0/-3.7 mmHg), aerobic exercise (-4.6/-2.4 mmHg), alcohol restriction (-3.8/-3.2 mmHg) and salt restriction (-3.6/-2.5 mmHg).

CLINICAL TRIALS

There are a number of placebo-controlled studies that have demonstrated significant benefits of ω3 fatty acids on blood pressure in hypertensive patients (41,45,64,68,77). Prisco et al (67) showed that taking 3.44 g/day of ω3 fatty acids for 2 months reduced 24 hour ambulatory blood pressure by -6/-5 mmHg in mild essential hypertensive, normolipidaemic men. Toft et al (80) also confirmed that in essential hypertensives the reduction in blood pressure was 3.8/2.0 mmHg greater than in controls after 16 weeks of a 4g/day fish oil supplement containing 85% EPA plus DHA. In a population

based study involving untreated mildly hypertensives randomised to 6g/day of 85% EPA and DHA or 6 g/day corn oil for 10 weeks, blood pressure fell -6.4/-2.8 mmHg with fish oil relative to the corn oil control group (5). The fall in blood pressure was inversely related to baseline plasma phospholipid ω3 fatty acids.

Recent data from the International Study of Macro- and Micro-nutrients and Blood Pressure (INTERMAP) of 4680 men and women aged 40-59 years from 17 population-based samples from China, Japan, United Kingdom and United States, confirmed an inverse, albeit weak, relationship between ω3 fatty acid intake and blood pressure (81). Interestingly the study showed a stronger association in non-hypertensive people and persons not experiencing dietary/medical intervention, a finding the authors ascribed to the removal of possible bias.

The blood pressure-lowering effects of ω3 fatty acids are potentiated by concomitant sodium restriction (17). Singer et al (78) also showed that fish oils amplified the hypotensive action of the β-adrenergic receptor blocker propranolol in mild-to-moderate hypertensives. In contrast, ACE inhibition (39) or combination therapy (29,49,86) provided no additional benefit in hypertensives. However, Lungershausen et al (48) showed that fish oils may be a useful adjunct to antihypertensive therapy with β-blockers or diuretics. Blood pressure was reduced by -3.1/-1.8 mmHg in treated hypertensives who were taking β-blockers alone, diuretics alone or a combination of the two.

In a randomised controlled trial, Vandongen et al (82) compared the effects of fish meals or fish oil supplements providing 2.2-6.3 g/day (mean intake 3.65 g/day) ω3 fatty acids for 12 weeks, in the setting of either a high or low fat diet in 120 men with high-normal blood pressure. In all the groups combined there was a significant inverse correlation between the fall in SBP and DBP and heart rate, and increases in long-chain ω3 fatty acids and decreases in long-chain ω6 fatty acids in platelet phospholipids.

Bao et al (2) examined whether dietary ω3 fatty acids had independent and / or additive effects to weight control on blood pressure. In a study of factorial design, 63 overweight treated hypertensives were randomised to a calorie-restricted weight loss program, a daily fish meal providing approximately 3.65 g/day ω3 fatty acids, the two regimens combined, or a control diet, for 4 months. The final 4 weeks involved a weight stabilisation period for the weight control groups whose weight fell on average 5.6 kg. Analysis of 24 hour ambulatory blood pressures showed significant independent and additive effects of dietary fish and weight loss. Relative to the control group, daytime blood pressures fell -6.0/-3.0 mmHg in the fish group, -5.5/-2.2 in the weight loss group and -13.0/-9.3 with the combined regimens. Fish consumption alone or in combination with weight loss also associated with significant reductions in heart rate (3-4 bpm), suggesting an autonomic/cardiac component to the blood pressure reduction.

Dokholyan et al (20) tested whether low doses of ω3 fatty acids would be effective in reducing blood pressure in patients with high-normal DBP or stage 1 hypertension (DBP 85-94 mmHg). The authors were, however, unable to show any fall in blood pressure following a 12 week intervention providing 0.48g EPA and 0.12g gamma-linolenic acid per day. These findings and the abovementioned data from trials in which ω3 fatty acids have reduced blood pressure, suggest that relatively high doses of ω3 fatty acids (> 3g/day) are required for blood pressure reduction.

Studies in humans have shown DHA and EPA have differential effects on cardiovascular risk factors (59) such as lipid metabolism (31,55,69,88) and platelet aggregation (87). Additionally blood pressure and heart rate are differentially affected by EPA and DHA (54). Mori et al showed in overweight, mildly-hypercholesterolaemic subjects, that 4g daily of highly purified DHA, but not EPA, supplemented for 6 weeks, significantly reduced 24-hr (-5.8/-3.3 mmHg) and daytime (awake) (-3.5/-2.0 mmHg) blood pressure, relative to olive oil (54). The blood pressure changes with DHA supplementation were accompanied by significant improvements in endothelial and smooth muscle function as well as reduced vasoconstrictor responses, in the forearm microcirculation (58). In addition, DHA, but not EPA, significantly reduced 24 hour, awake and asleep heart rate (54). These findings contrast with those reported by Woodman et al (88) who showed that neither EPA nor DHA given as 4g daily for 6 weeks, decreased blood pressure in treated hypertensive Type 2 diabetic patients. Possible explanations for the lack of an antihypertensive effect in the latter trial could be related to concomitant use of other pharmacologic agents, the presence of glycaemia

and increased blood pressure variability in the diabetic patients.

MECHANISMS

The mechanisms for the antihypertensive effects of ω3 fatty acids are likely to be multifactorial involving effects on vascular, cardiac and/or autonomic function. These and other possible mechanisms will be addressed in detail below.

Vascular Function

Insight into how ω3 fatty acids might affect blood pressure and vascular function were first demonstrated in studies using animal models. Fish oils supplemented to hypertensive rats increased endothelial relaxation in aortic rings exposed to acetylcholine (89) and decreased pressor reactivity of perfused mesenteric resistance vessels (16). Yin et al (89) demonstrated that in spontaneously hypertensive rats (SHR) increased endothelial relaxation following ω3 fatty acids was due, at least in part, to suppression of thromboxane A_2 (TXA_2) or cyclic endoperoxides, and enhanced endothelial nitric oxide (NO) synthesis. In humans, fish oils reduced forearm vascular reactivity to angiotensin II and noradrenaline (13,47,91). Furthermore, indomethacin given orally blunted the effect of fish oils on noradrenaline and angiotensin II responses in human forearm resistance arteries, suggesting that ω3 fatty acids, at least in part, modify cyclooxygenase-derived prostanoids (12). Of note, indomethacin alone, at the same dose, did not affect responses to angiotensin II or noradrenaline (12).

Fish oils were shown to have a minimal effect on acetylcholine- or reactive hyperaemia-induced vasodilation in the forearm resistance arteries of healthy subjects (12). In contrast, ω3 fatty acids improved impaired responses to endothelium-dependent vasodilators in patients with coronary artery disease (24,83). Similar effects were demonstrated in animal models characterized by endothelial damage, including the SHR (89) and the glucocorticoid-induced hypertensive rat (90), as well as in the hypercholesterolaemic and atherosclerotic pig (76). The vasodilatory responses to acetylcholine in hypercholesterolaemic subjects were also enhanced by dietary fish oil in the absence of changes in total cholesterol (10).

McVeigh et al (53) showed that 10g daily ω 3 fatty acids supplemented for 6 weeks to individuals with Type 2 diabetes improved forearm vasodilator responses to acetylcholine, but not to glyceryl trinitrate. These data suggest that fish oils may protect against vasospasm and thrombosis by enhancing NO release and suppressing thromboxane. Additional evidence that ω3 fatty acids affect the production and/or release of NO was from studies conducted by Shimokawa et al (75), who showed enhanced responses to endothelium-dependent vasodilators such as bradykinin, serotonin, ADP and thrombin, in rings of coronary arteries taken from pigs fed cod-liver oil. *In vitro* studies have also shown that EPA potentiates NO release evoked by IL-1β in vascular smooth muscle cells (71) and in endothelial cells in response to ADP and bradykinin (6).

In humans, ω3 fatty acids improve endothelial function in systemic large arteries. In this regard, Goodfellow et al (28), showed significant improvements in flow-mediated dilatation of the brachial artery in hyperlipidaemic subjects given 4g daily of ω3 fatty acids for 4-months. The improvement was confined to endothelial-dependent responses.

A number of studies in rats have demonstrated differential effects of EPA and DHA on vascular function (21,51). Engler et al (21), showed that in aortic rings EPA and DHA induced endothelium-dependent and independent vasodilation, respectively. Using aortas from SHR, McLennan et al (51) demonstrated DHA was also more effective than EPA at inhibiting thromboxane-like vasoconstrictor responses. The authors suggested that DHA prevented thromboxane-induced contraction and restored the vasoconstrictor/vasodilator balance following impairment of the normal NO-related processes.

Harris et al (34) provided indirect evidence for a beneficial effect of DHA, but not EPA, on endothelial function in humans by measuring serum and urinary nitrate output. However, these results are only suggestive of increased nitric-oxide production in endothelial cells, given that nitrates can also derive from other sources.

More definitive evidence for differential effects of EPA and DHA on vascular function in humans was provided by Mori et al (58). They showed that in overweight subjects with hyperlipidaemia, DHA, but not EPA, improved vasodilator responses to endogenous and exogenous NO donors and attenuated vasoconstrictor response to noradrenaline in the forearm microcirculation (58). The mechanisms

were predominantly endothelium-independent, based on the fact that co-infusion of acetylcholine with L-NMMA and infusion of nitroprusside, both of which are endothelium-independent, resulted in enhanced vasodilatory responses. However, the data do not preclude an endothelial component in the dilatory responses associated with DHA. Mori et al also demonstrated that improved vascular function following supplementation with DHA, but not EPA, was associated with a reduction in blood pressure (54). Similarly, Yin et al (89) showed that in perfused mesenteric resistance vessels from SHR ω3 fatty acids had an endothelial-independent vasodilatory effect.

The effects of ω3 fatty acids, particularly those of DHA, on vasoreactivity are likely due to direct and indirect effects on the arterial wall (58). Incorporation of ω3 fatty acids into endothelial membranes could increase membrane fluidity, calcium influx, and endogenous synthesis and release of NO. Experimental evidence also suggests ω3 fatty acids may have direct effects on receptor-stimulated NO release, as well as enhanced release of vasodilator prostanoids and/or endothelial-derived hyperpolarizing factor (90). Furthermore, enhanced vasodilator response to sodium nitroprusside could be related to increased biotransformation to NO or increased reactivity of smooth muscle cells to vasorelaxation as a result of decreased calcium influx (11). In the study of Mori et al (58), increased release of cyclooxygenase-derived vasodilatory metabolites could have accounted for the decreased vasoconstrictor response to noradrenaline following DHA. The vasodilator effects of DHA may also be related to increased basal production of NO in smooth muscle cells consequent to decreased release of platelet-derived growth factor (PDGF) (25). It has been shown that PDGF inhibits induction of NOS in vascular smooth muscle cells (72).

Vascular Compliance

It is well recognized that blood pressure is strongly affected by arterial compliance, which in turn is influenced by endothelial function. In this regard, McVeigh et al (52) showed that in Type 2 diabetic individuals compliance in the large arteries and more peripheral vasculature improved significantly after 6 weeks of fish oil compared with olive oil. EPA and DHA supplementation also improved arterial compliance by 35% and 27%, respectively, in patients with dyslipidaemia (62).

The role of Vasodilator and Vasoconstrictor Prostanoids

The antihypertensive effect of ω3 fatty acids are likely mediated, in part, by modulation of vasodilator and vasoconstrictor prostanoids. ω3 Fatty acids suppress production of TXA_2 a vasoconstrictor and aggregator (22). Knapp et al (42) showed that in patients with atherosclerosis diets rich in ω3 fatty acids decreased TXA_2 with concomitant increased TXA_3, the analogous but substantially less biologically active EPA-derived metabolite. Others have reported an increase in prostaglandin I_3 (PGI_3, otherwise known as prostacyclin), derived from EPA and equipotent in its vasodilatory and anti-aggregatory activities to prostaglandin I_2 (PGI_2), without a fall in PGI_2, following ω3 fatty acids (23,42). It has been suggested that an overall increase in total prostacyclin (PGI_2 and PGI_3) formation in conjunction with reduced total thromboxane (TXA_2 and TXA_3), could favourably alter endothelial and vascular responses following dietary ω3 fatty acids.

Cardiac Function

Studies employing dietary fish or ω3 fatty acid supplements have often resulted in a reduction in heart rate in animals (4,50) and humans (2,18,30,54,82,88), suggesting a significant cardiac component associated with the antihypertensive effects. This is likely mediated by effects on autonomic nerve function or β-adrenoreceptor activity. In a meta-analysis of 30 studies Mozaffarian et al (61) showed that ω3 fatty acids reduce heart rate overall by -1.6 bpm, with a greater reduction in trials with baseline heart rate $\geq$69 bpm (-2.5 bpm) and those of $\geq$12 weeks duration (-2.5 bpm).

In overweight treated hypertensives a daily fish meal alone or in combination with a calorie-restricted weight loss program, significantly reduced 24 hour (-3.1 bpm) and awake (-4.2 bpm) ambulatory heart rates (2). In overweight, mildly hyperlipidaemic, but otherwise healthy men given 4g daily EPA, DHA or olive oil for 6 weeks, heart rate was reduced by DHA, but not EPA (54). 24 Hour, awake and asleep heart rate fell -3.5, -3.7 and -2.8 bpm, respectively, following DHA. Of note, EPA supplementation resulted in a small, but non-significant rise in heart rate. In Type 2 diabetic individuals, the same authors confirmed that DHA, but not EPA, significantly reduced clinic standing (-5.8 bpm)

and supine (-3.9 bpm) heart rates compared with placebo (88). These differential effects of EPA and DHA on heart rate responses in humans were supported by Grimsgaard et al (30). These finding are also supported by studies employing animal models. In Hooded Wistar rats fed purified oils, McLennan et al (51) showed that DHA, but not EPA, prevented ischaemia-induced cardiac arrhythmias.

Human studies also strongly suggest that ω3 fatty acids increase heart rate variability in patients at high risk of sudden cardiac death and in healthy individuals (14,15), supporting an antiarrhythmic effect of ω3 fatty acids.

The mechanisms through which ω3 fatty acids affect heart rate are likely related to their incorporation into myocardial cells and altering electrophysiological function in a manner that reduces the vulnerability to ventricular fibrillation (44). The anti-arrhythmic effects of ω3 fatty acids are due to their ability to inhibit the fast, voltage-dependent sodium current and the L-type calcium currents, although there is also evidence they modulate potassium channels (44). Interestingly, the free fatty acids and not phospholipid-bound fatty acids conferred the inhibitory effect (44).

The Role of Catecholamines

Data from animal studies suggest that the blood pressure-lowering effects of ω3 fatty acids may relate to modulation of catecholamines and ATP. Hashimoto et al (36) showed that DHA fed intragastrically to aged female Wistar rats resulted in reduced plasma noradrenaline levels and increased adenyl purines such as ATP, released both spontaneously and in response to noradrenaline from segments of caudal artery. Rats fed DHA at a dose of 300 mg/kg/day for 12 weeks had 44% lower plasma noradrenaline levels and the repression of the elevation in blood pressure observed with advancing age. Plasma adenyl purines were also significantly inversely associated with blood pressure. These findings are noteworthy given that ATP causes vasodilation by stimulating the release of NO from endothelial cells, by a direct action on vascular smooth muscle cells and by hyperpolarizing smooth muscle cells. It was suggested that DHA accelerated ATP release from vascular endothelial cells, in conjunction with reduced plasma noradrenaline, might contribute to the fall in blood pressure following ω3 fatty acid supplementation (36). Nishimura et al (63) also demonstrated ω3 fatty acids affect noradrenaline levels in diabetic rats. EPA given as 100 mg/kg/day for 6 weeks, increased urinary nitrate excretion and reduced cardiac noradrenaline concentrations compared with controls. Systemic administration of an NO inhibitor abolished these effects, suggesting that EPA may stimulate NO production and that increased NO could play a role in inhibiting enhanced cardiac sympathetic activity (63).

Effects on Membrane Function

A number of the abovementioned plausible mechanisms for the blood pressure-lowering effects of ω3 fatty acids are likely related to their incorporation into plasma and cellular membranes, with consequent alteration in the physicochemical structure of the membrane. It could be expected this would lead to changes in fluidity, flexibility, permeability and function of the membrane and membrane-bound proteins. It is also plausible this may affect enzyme activity, receptor affinity and transport capacity of the cell, including synthesis and/or release of NO. Hashimoto et al (35), demonstrated that DHA had a greater effect than EPA in increasing membrane fluidity of endothelial cells cultured from rat thoracic aortas. This observation may have significance in view of the greater effect of DHA than EPA on maintaining vascular function and reducing blood pressure in humans (54,58).

CONCLUSIONS

There is sound evidence that ω3 fatty acids taken as fish oil supplements or fish meals will reduce blood pressure. The fall in blood pressure is greater in hypertensive patients and those with high-normal blood pressure. The effects of ω3 fatty acids on blood pressure are also enhanced by moderation of salt intake. Although the effects of ω3 fatty acids on blood pressure are modest, increasing fish and/or fish oil consumption is likely to confer significant benefit. Lowering population average SBP by 2 mmHg has been estimated to result in reduced mortality rates of 6% for stroke and 4% for coronary heart disease (79).

Most populations prone to hypertension have a low intake of dietary ω3 fatty acids and increasing fish consumption to 2-4 serves per week is most likely to have cardiovascular benefits which may help protect against hypertension, coronary disease and ischaemic stroke (43,46). Smaller amounts providing 1-

1.5g per day ω3 fatty acids have an antiarrhythmic effect and provide secondary prevention against coronary death (27). In hypertensives some modest blood pressure reduction is likely to be gained with 3-4 g/day ω3 fatty acids. In hypertensive diabetics it is advisable to increase ω3 fatty acid intake with close monitoring of glycaemic control. The magnitude of the blood pressure reduction can become substantial when ω3 fatty acids are incorporated into a weight reducing program (2) or when increased ω3 fatty acid consumption is part of a broader dietary change including increased consumption of fruits and vegetables, and moderation of salt intake (70).

Other articles in this theme issue include references (92-103).

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